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FEE TRANSMITTAL
For FY 2008

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($)	540.00

Complete if Known	
Application Number	10/018,373
Filing Date	December 6, 2001
First Named Inventor	Hans BIGALKE
Examiner Name	Vanessa L. FORD
Art Unit	1645
Attorney Docket No.	MERZ 32 PCT US

METHOD OF PAYMENT (check all that apply)

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☑ Deposit Account Deposit Account Number: 08.3220 Deposit Account Name: Hueschen and Sage

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	310	155	510	255	210	105	
Design	210	105	100	50	130	65	
Plant	210	105	310	155	160	80	
Reissue	310	155	510	255	620	310	
Provisional	210	105	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	210	105
Multiple dependent claims	370	185

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 20 or HP =	_____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
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4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Filing a Brief in Support of an Appeal under 37 CFR § 41.20(b)(2)	540.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 37,710	Telephone 269.382.0030
Name (Print/Type)	G. PATRICK SAGE		Date March 4, 2009

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Applicant: Hans BIGALKE and Jürgen FREVERT
Application Serial No. 10/018,373
Title: THERAPEUTIC COMPOSITION COMPRISING A BOTULINUM NEUROTOXIN
Filed: December 6, 2001

CERTIFICATE OF MAILING BY EXPRESS MAIL SERVICE UNDER 37 CFR § 1.10

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THE FIRM OF HUESCHEN AND SAGE

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	Hans BIGALKE and Jürgen FREVERT
Serial No.:	10/018,373
Filed:	December 6, 2001
For:	Therapeutic Composition Comprising a Botulinum Neurotoxin
Art Unit:	1645
Examiner:	Vanessa L. FORD

REPLY BRIEF ON BEHALF OF APPELLANT UNDER 37 CFR § 41.41

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INTRODUCTORY COMMENTS

In response to the Examiner's Answer, dated January 6, 2009, with regard to the above-identified application, Appellant submits the following arguments in reply to the Examiner's arguments in connection with the grounds of rejection of the appealed claims.

APPELLANT'S REPLY ARGUMENTS

1. Rejection of claims for obviousness over the disclosure of *Keen, et al.* in view of *Johnson, et al.*

Appellant has demonstrated that the Examiner has not established a *prima facie* case of obviousness because the Examiner has failed to establish that all limitations of the instant claims are taught or suggested by the cited art, and that the Examiner has not identified a suggestion or motivation to combine the teaching of the prior art references.

The Examiner has maintained that Appellant's claims are *prima facie* obvious. The following remarks are submitted in response to particular points raised in the Examiner's Answer.

1.1 Appellant has rebutted *prima facie* obviousness on the basis that the cited art do not teach or suggest all claim limitations.

It is well-settled that to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Appellant has demonstrated that the cited art do not teach or suggest the instant generic claim limitation to administering a botulinum neurotoxin preparation to a subject, "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes" at **Section A1a** beginning at page 8 of Appellant's Brief of October 7, 2008.

The Examiner does not provide comment or an explanation of the reasons for disagreement with respect to Appellant's assertions in Section A1a of Appellant's Brief in accord with MPEP § 1207.02(A)(10).

Moreover, MPEP § 1207.02 states that an Examiner's Answer filed in response to an Appeal Brief must comply with MPEP guidelines. In particular, MPEP § 1207.02(A)(9)(d) requires that for each rejection under 35 U.S.C. § 103 the examiner is required to point out where each of the specific limitations recited in the claims is found in the prior art, explain the differences between the rejected claims and the prior art, and explain why it would have been obvious to have modified the primary reference to arrive at the claimed subject matter. Moreover, according to MPEP § 1207.02(A)(9)(e), where there are questions as to how limitations in the claims correspond to features in the prior art, the examiner must compare at least one of the rejected claims feature by feature with the prior art relied on in the rejection as required under MPEP § 1207.02.

Appellant submits that the Examiner fails to point to where the specific limitation to treating subjects who already exhibit neutralizing antibodies to botulinum neurotoxin complexes may be found in the cited art, has not fulfilled her obligation to properly construe all claim limitations in view of the cited art, and moreover, has failed to identify where each of the specific limitations recited in the claims, for example, administering a botulinum neurotoxin to a subject "wherein the human or animal subject already exhibits neutralizing antibodies against neurotoxin complexes", is found in the cited art, as required under MPEP § 1207.02.

Appellant has, however, demonstrated that the cited art do not teach or suggest the instant claim limitation to a therapeutic method of treatment with a botulinum neurotoxin preparation "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes" for the fact that

the cited art teach futility in treating subjects who already exhibit neutralizing antibodies. For example, *Keen, et al.* teach that, "The antibodies can render the toxin ineffective but do not harm the patient." (see page 98). *Johnson, et al.* state that, "The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective." (see Column 1, lines 51-55).

Nonetheless, the Examiner acknowledges that, "*Keen, et al.* teach that patients that receive large dosages of botulinum toxin complex over long periods of time can render the toxin non-effective (e.g. these patients are non-responders)." (See Examiner's Answer at page 18.) Moreover, the Examiner acknowledges that, "*Johnson, et al.* teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective." (See Examiner's Answer at page 21.)

The cited art teach that the presence of neutralizing antibodies in subjects renders administration of botulinum neurotoxin compositions to such subjects ineffective, which teaching is acknowledged by the Examiner. Therefore, the cited art, *Keen, et al.* and *Johnson, et al.*, may in no way be construed to teach or suggest the claim limitation to administering a botulinum neurotoxin to a subject "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes". The criticality of such limitation is the subject of Appellant's application, an advance in the treatment of patients who are non-responsive to conventional botulinum neurotoxin therapy and which treatment meets the unsolved needs of patients exhibiting neutralizing antibodies and who have been heretofore untreatable with botulinum neurotoxin therapy.

Therefore, the Examiner's rejection should be reversed for failing to demonstrate all claim limitations to be taught or suggested by the art. Absent such showing, the Examiner has not met her burden to demonstrate that the rejected claims are

prima facie obvious after repeated solicitations from Appellant, as well as not having met her burden in response to an Appeal Brief under MPEP § 1207.02.

1.2 Appellant's claims are not *prima facie* obvious.

It is well-settled that a *prima facie* rejection for obviousness in view of the combined reference disclosures is only established if there is some suggestion or motivation to combine the prior art reference disclosures, and the teaching or suggestion to make the combination, together with a reasonable expectation of success, must both be found in the prior art, not based on Applicant's own disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

In response to Appellant's demonstration that there is no suggestion to combine the teaching of the prior art references, the Examiner opines that, "One of ordinary skill in the art would reasonably conclude that the compositions taught by *Johnson, et al.* comprise botulinum toxin formulations that lessen or reduce neutralizing antibodies because it contains essentially pure botulinum toxin. *Johnson, et al.* recognize patients that have developed neutralizing antibodies to the complex are a growing concern in the art, thus this is the very bases for the development of compositions comprising essentially pure botulinum toxin. Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex." (See Examiner's Answer at page 19.)

The Examiner and Appellant agree that *Johnson, et al.* teach a botulinum neurotoxin preparation which lessens the possibility of antibody formation in patients.

The Examiner's conclusion, however, that, "Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing

antibodies to the botulinum toxin complex" is not substantiated. The Examiner fails to identify a teaching or suggestion in *Keen, et al.* and *Johnson, et al.* to administer a botulinum neurotoxin composition to a subject who already exhibits neutralizing antibodies, as recited in the instant claims.

The Examiner further opines that *Keen, et al.* teach that, "It is well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies" and that, "*Johnson, et al.* also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex." The Examiner concludes that, "*Johnson, et al.* provided a solution to this problem by preparing a product that is pure neurotoxin instead of the complex." (See Examiner's Answer at pages 19- 20.)

The Examiner, again, points to teaching in which *Johnson, et al.* solve the problem of developing neutralizing antibodies by preparing a product that is pure neurotoxin instead of the complex.

The Examiner goes on to conclude that, "Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition." (See Examiner's Answer at page 20.)

The Examiner's conclusions regarding the suggestion or motivation to combine the teaching of the prior art, reiterated above, evidences the Examiner's misunderstanding of the standard for *prima facie* obviousness.

The instant enquiry is whether, based on *Keen, et al.* and *Johnson, et al.*, it would have been obvious to administer a botulinum neurotoxin which is free from complexing proteins which naturally form complexes with botulinum neurotoxins to patients already exhibiting neutralizing antibodies. This is the subject matter of the claims, not whether a composition may be expected to reduce the possibility of developing neutralizing antibodies.

The Examiner does not articulate a factual basis to support a conclusion that *Johnson, et al.* developed compositions of essentially pure botulinum toxin to overcome the problem of treating patients who already exhibit neutralizing antibodies.

In fact, the Examiner identifies teaching in the cited art that administration of a botulinum neurotoxin composition to subjects who already exhibit neutralizing antibodies is well recognized not to be effective. The Examiner cites *Johnson, et al.*, at Column 1, for teaching, "The toxin is recognized by the patient's immune systems as foreign and stimulates antibody production. *Johnson, et al. teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective.*" (See Examiner's Answer at page 21, emphasis added). Furthermore, the Examiner acknowledges that, "*Keen, et al.* teach that antibodies to botulinum toxin A have been described in patents receiving much larger dosages of botulinum toxin complex for long periods of time and the antibodies can render the toxin non-effective but do not harm the patient (nonresponders) (page 98)." (See the November 5, 2007 Office Action at page 7 and the Examiner's Answer at page 18.)

Furthermore, Appellant has demonstrated that the *Keen, et al.* and *Johnson, et al.* disclosures teach that subjects who have developed neutralizing antibodies would not benefit from treatment with botulinum neurotoxins. Appellant has quoted *Johnson, et al.* for teaching, "The toxin is recognized by patient's immune

systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective." (see Column 1, lines 51-55 and Appellant's Appeal Brief of October 7, 2008 at page 16).

Moreover, it is the position of the Examiner that Appellant has mischaracterized this teaching in *Johnson, et al.* The Examiner concludes that, "The statement regarding '*Johnson, et al.* teach that this renders treatment of various hyperactive muscle disorders with botulinum toxin ineffective' refers to the previous products of the art, e.g. botulinum toxin complex (containing neutralizing antibodies) (e.g. BOTOX®) which includes complexing proteins. This statement does not refer to the ineffectiveness of the products taught by *Johnson, et al.*" (See Examiner's Answer at page 22).

To clarify, Appellant acknowledges that *Johnson, et al.* discuss the state of the art with regard to botulinum neurotoxin therapy teaching that, "A major drawback to the use of botulinum toxin in treatment of hyperactive muscle disorders is development of antibodies or other types of immunity by patients. The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin *ineffective*." (see *Johnson, et al.*, Column 1, lines 49-55, *emphasis added*). In contrast to the Examiner's position, *Johnson, et al.* are not specifically referring "to the previous products of the art". Rather, *Johnson, et al.* conclude that the manifestation of neutralizing antibodies renders treatment with botulinum neurotoxin, regardless of the preparation, ineffective.

Appellant has demonstrated with the cited art, *Keen, et al.* and *Johnson, et al.*, that it is well accepted in the art that administering *Clostridium botulinum* neurotoxin, regardless of the preparation, to patients who have already developed neutralizing antibodies is ineffective. The cited art do not teach or

suggest administration of botulinum neurotoxin, regardless of the preparation, in subjects who already exhibit neutralizing antibodies against botulinum neurotoxin with an expectation that such administration would be effective. This explicit teaching in the cited art with regard to the ineffectiveness of botulinum neurotoxin therapy in subjects already exhibiting neutralizing antibodies may not be disregarded and *Keen, et al.* and *Johnson, et al.* do not provide a solution.

Appellant submits that the factual information in the art of record regarding the ineffectiveness of botulinum neurotoxin treatment in subjects with neutralizing antibodies against botulinum neurotoxin is consistent and clear. The Examiner's speculation that, "Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition" is nothing more than speculation and finds no basis in the prior art disclosure of record.

1.3 The Examiner misapplied and fails to substantiate a finding of obviousness under *KSR International Co. v. Teleflex Inc.*

The Examiner attempts to recite exemplary rationales to support a finding of obviousness. The Examiner states that "Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) discloses that if a technique has been used to improve one method and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill." Furthermore, the Examiner states that, "*KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that 'The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.'" (See Examiner's Answer at pages 19 and 23).

The Examiner opines that, "In the instant case, compositions comprising botulinum toxin without complexing proteins are known in the art. See *Johnson, et al.* It is also known in the art that patients develop neutralizing antibodies. See *Keen, et al.*" The Examiner, therefore, concludes that, "Thus, it would be obvious to use a known product in a known method that would do more than predictable results." (See Examiner's Answer at page 23.)

The Examiner does not substantiate the conclusion with factual information, for example, the Examiner does not identify a method which has been shown in the art to be effective in treating patients exhibiting neutralizing antibodies. The Examiner does not identify which methods predict therapeutic efficacy in patients exhibiting neutralizing antibodies. The Examiner does, however, point to teaching that patients who develop neutralizing antibodies are known as "non-responders" and that botulinum neurotoxin treatment in these subjects is ineffective.

Appellant rebuts the Examiner's conclusions that the instant invention is obvious based on the Examiner's limited reasoning. According to MPEP § 2143 interpreting *KSR*, the Examiner must demonstrate a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable.

The Examiner has failed to articulate a finding that the result of the combination of prior art elements according to known methods would be predictable to one of ordinary skill in the art in several iterations of the rejection for obviousness based on MPEP interpretation of *KSR*.

Appellant has, however, demonstrated that it is well-accepted that antibodies to botulinum toxin render treatment with botulinum neurotoxin ineffective.

Moreover, Appellant submits that the Examiner has not articulated reasoning within the *KSR* guidelines as to why it would be obvious to administer a botulinum neurotoxin preparation to subjects already exhibiting neutralizing antibodies. The teaching of record only describes administration of botulinum toxin without complexing proteins for preventing the development of neutralizing antibodies. For example, *Johnson, et al.* teach that, "One way to reduce the number of patients developing neutralizing antibodies would be to develop a more shelf-stable product with a higher specific activity following lyophilization" and also teach that, "This improvement also reduces the amount of inactive toxin (toxoid) in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients". (See *Johnson, et al.* at Column 1, lines 55-58 and Column 2, lines 47-51.)

Furthermore, the Examiner has not articulated a finding that one of ordinary skill in the art would have recognized that the results of the combination of prior art elements were predictable in accord with *KSR* guidelines, particularly in view of the *Johnson, et al.* and *Keen, et al.* teaching that patients who develop neutralizing antibodies no longer respond to botulinum toxin treatment. MPEP § 2143 guides that if any of these findings cannot be made, then the exemplary rationale cannot be used to support a conclusion of obviousness.

Appellant submits that the Examiner's basis for obviousness under the *KSR* exemplary rationale cannot be sustained by perfunctory statements and speculation.

Furthermore, an exemplary rationale recited by the Examiner as to why the claimed invention would have been obvious in view of *KSR* is that it would be, "obvious to try". (See Examiner's Answer at pages 20 and 24.)

To support this further exemplary rationale, the Examiner finds that, "In the instant case, there is a need in the art to find a solution to the problem of development of neutralizing antibodies in patients administered botulinum toxin complex over long periods of time. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection has failed." Without any actual basis, the Examiner goes on to conclude that, "*Johnson, et al.* developed compositions of essentially pure botulinum toxin to overcome these problems recognized in the prior art." (See Examiner's Answer at page 20.)

Similarly without basis, the Examiner concludes that, "In the instant case, it would be obvious to administer pure botulinum toxin to patents that have neutralizing antibodies because *Johnson, et al.* teach that the compositions of the invention reduces the chances of patients developing neutralizing antibodies. " (See Examiner's Answer at page 25.)

According to MPEP § 2143 a proper basis under the "obvious to try" exemplary rationale to support a finding of obviousness requires the Examiner to articulate a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem and that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success. Moreover, the Examiner is instructed to make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

In the instant case, such solutions are described in the claims to provide a means for treating patients exhibiting neutralizing antibodies. The Examiner has, in fact, identified NO predictable potential solutions to the problem of treating subjects who already exhibit neutralizing antibodies against neurotoxin complexes. As discussed above, the cited art teach that neutralizing antibodies directed against botulinum neurotoxin are the cause of therapeutic failure and that subjects who

exhibit neutralizing antibodies would not benefit from treatment with botulinum neurotoxin.

Appellant submits that the Examiner's conclusion is precisely the product of an impermissible hindsight reconstruction. The Examiner has not provided any basis in fact as to why one skilled in the art would administer botulinum neurotoxin in view of the prior art teaching that such administration would not be effective, nor has the Examiner identified predictable potential solutions to the problem of treating subjects already exhibiting neutralizing antibodies.

Not only has the Examiner failed to identify any predictable potential solutions to the problem of treating subjects who already exhibit neutralizing antibodies against neurotoxin complexes, the Examiner has not articulated a finding that one of ordinary skill in the art could have pursued known potential solutions with a reasonable expectation of success. MPEP § 2143 guides that
if any of these findings cannot be made, then the exemplary rationale cannot be used to support a conclusion of obviousness.

Appellant has demonstrated that the Examiner's recitation of exemplary *KSR* bases for obviousness, namely that the instant method of treating subjects who already exhibit neutralizing antibodies against neurotoxin complexes with botulinum neurotoxin which is free of complexing proteins is "obvious to try", is not substantiated.

Appellant submits that the Examiner has not made of record prior art disclosure which fulfills the requirements of MPEP § 2143 interpretation of *KSR* and has capriciously misapplied *KSR* and has prejudicially misrepresented the art of record.

Appellant submits that the Examiner has failed to establish a factual basis for finding that the instant claims are obvious. Absent such showing, the Examiner has not met her burden to demonstrate that the rejected claims are *prima facie* obvious.

2. Rejection of claims for obviousness over the disclosure of *Carruthers, et al.* in view of *Heckman, et al.* and further in view of *Johnson, et al.*

2.1 Appellant has rebutted *prima facie* obviousness on the basis that the cited art do not teach or suggest all claim limitations.

Appellant has demonstrated that the cited art do not teach or suggest the instant generic claim limitation, "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes" at **Section B1a** beginning at page 24 of Appellant's Brief of October 7, 2008.

The Examiner does not provide comment with regard to Appellant's assertions in Section B1a, that the cited art do not teach the instant claim limitation, "wherein the human or animal already exhibits neutralizing antibodies against neurotoxin complexes".

The Examiner acknowledges that, "*Carruthers, et al.* and *Heckman, et al.* teach do not teach the claim limitation 'wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes'. However, *Johnson, et al.* teach compositions of pure botulinum toxin that are free from non-complexing proteins." (See Examiner's Answer at page 28.)

Appellant submits that the Examiner has not fulfilled her obligation to properly construe all claim limitations in view of the cited art under MPEP § 1207.02, and moreover, has failed to identify where each of the specific limitations recited in the claims, for example, administering a botulinum neurotoxin preparation to a subject, "wherein the human or animal subject already exhibits neutralizing antibodies against neurotoxin complexes", is found in the cited art (i.e., *Johnson, et al.)*.

Appellant has demonstrated that *Johnson, et al.* do not teach or suggest the instant claim limitation to a therapeutic method of treatment with a botulinum neurotoxin preparation, "wherein the human or animal subject already exhibits neutralizing antibodies against neurotoxin complexes", and that the cited art is completely silent with respect to administering a botulinum neurotoxin composition, "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes."

The Examiner's rejection should be reversed as failing to establish a *prima facie* case of obviousness.

2.2 Appellant's claims are not *prima facie* obvious.

The Examiner has not established a *prima facie* case of obviousness because the Examiner has not identified a suggestion or motivation to combine the teaching of the prior art references. What is more, the cited art actually suggest that such treatment would not be successful.

Appellant has demonstrated that *Johnson, et al.* teach that, "A major drawback to the use of botulinum toxin in treatment of hyperactive muscle disorders is development of antibodies or other types of immunity by patients. The toxin is recognized by patient's immune systems as foreign and stimulates antibody

production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective." (See Column 1, lines 49-55, emphasis added.), which teaching is acknowledged by the Examiner at page 31 of the Examiner's Answer. Furthermore, the Examiner acknowledges that, "*Carruthers, et al.* teach that in neurologic patients, it is estimated that one-third of all treatment failures may be the result of the development of antibodies (page 214)." (See Examiner's Answer at page 27, emphasis added.)

Carruthers, et al. and *Johnson, et al.* teach that administration of botulinum neurotoxin compositions to subjects already exhibiting neutralizing antibodies against botulinum neurotoxins would not be successful. Therefore, there is no teaching in the cited art which would provide one skilled in the art with any motivation to administer a botulinum neurotoxin composition with the expectation that such composition would provide efficacy in subjects already exhibiting neutralizing antibodies.

Appellant submits that the factual information in the art of record regarding the ineffectiveness of botulinum neurotoxin treatment in subjects with neutralizing antibodies against botulinum neurotoxins, as discussed above, does not provide one skilled in the art with a reasonable expectation of success for treating a subject already exhibiting neutralizing antibodies against botulinum neurotoxins with botulinum neurotoxin preparations, wherein the neurotoxin is free of complexing proteins.

The Examiner's rejection should be reversed as failing to establish a *prima facie* case of obviousness.

2.3 The Examiner misapplied and fails to substantiate a finding of obviousness under *KSR International Co. v. Teleflex Inc.*

The Examiner attempts to recite exemplary rationales to support a finding of obviousness. The Examiner states that "Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) discloses that if a technique has been used to improve one method and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill." Furthermore, the Examiner states that, "*KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that 'The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.'" (See Examiner's Answer at pages 29 and 32).

The Examiner opines that, "In the instant case, compositions comprising botulinum toxin without complexing proteins are known in the art. See *Johnson, et al.* It is also known in the art that patients develop neutralizing antibodies. See both *Carruthers, et al.* and *Johnson, et al.* It is known in the art to use botulinum toxin to treat hyperhidrosis. See *Heckman, et al.* Thus, it would be obvious to use a known product in a known method that would do more than yield predictable results." (See Examiner's Answer at page 33.)

Appellant submits that the Examiner has not articulated a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable, which finding is required under MPEP § 2143 interpretation of the *KSR*.

Appellant has, however, demonstrated that an ordinary practitioner would not have expected or predicted that administering botulinum neurotoxin preparations to subjects who already exhibit neutralizing antibodies to botulinum neurotoxin would provide an effect in these subjects for the fact that the cited art teach that antibodies to botulinum toxins renders treatment with the toxin ineffective.

Appellant has demonstrated that *Carruthers, et al.* and *Johnson, et al.* teach that the presence of neutralizing antibodies directed against botulinum neurotoxin renders the toxin ineffective and are the cause of therapeutic failure in subjects who exhibit neutralizing antibodies, thereby negating predictability with respect to treating subjects already exhibiting neutralizing antibodies with botulinum neurotoxins. This explicit teaching in the cited art with regard to the ineffectiveness of botulinum neurotoxin therapy and treatment failure in subjects already exhibiting neutralizing antibodies discredits the use of botulinum neurotoxin therapy in such subjects, thereby teaching away from administering botulinum neurotoxin in subjects already exhibiting neutralizing antibodies.

Furthermore, an exemplary rationale recited by the Examiner as to why the claimed invention would have been obvious in view of *KSR* is that it would be, "obvious to try". (See Examiner's Answer at pages 29 and 33.)

To support the exemplary rationale, the Examiner finds that, "In the instant case, there is a need in the art to find a solution to the problem of development of neutralizing antibodies in patients administered botulinum toxin complex over long periods of time. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection has failed." The Examiner, therefore, concludes that, "*Johnson, et al.* developed compositions of essentially pure botulinum toxin to overcome these problems recognized in the prior art." (See Examiner's Answer at page 30.)

Furthermore, the Examiner concludes that, "In the instant case, it would be obvious to administer pure botulinum toxin to patents that have neutralizing antibodies because *Johnson, et al.* teach that the compositions of the invention reduces the chances of patients <u>developing neutralizing antibodies</u>. " (See Examiner's Answer at page 34, <u>emphasis added</u>.)

According to MPEP § 2143, a proper basis under the "obvious to try" exemplary rationale to support a finding of obviousness requires the Examiner to articulate a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem and that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success. Moreover, the Examiner is instructed to make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

In the instant case, such solutions are described in the claims to provide a means for treating patients exhibiting neutralizing antibodies. The Examiner has, in fact, identified NO predictable potential solutions to the problem of treating subjects who already exhibit neutralizing antibodies against neurotoxin complexes. As discussed above, *Johnson, et al.* and *Carruthers, et al.* teach that neutralizing antibodies directed against botulinum neurotoxin are the cause of therapeutic failure and that subjects who exhibit neutralizing antibodies would not benefit from treatment with botulinum neurotoxin, i.e., there are NO identified predictable potential solutions to treating subjects already exhibiting neutralizing antibodies.

Appellant submits that the Examiner's conclusion is precisely the product of an impermissible hindsight reconstruction. The Examiner has not provided any basis in fact as to why one skilled in the art would administer botulinum neurotoxin in view of the prior art teaching that such administration would not be effective, nor has the Examiner identified predictable potential solutions to the problem of treating subjects already exhibiting neutralizing antibodies.

Not only has the Examiner failed to identify any predictable potential solutions to the problem of treating subjects who already exhibit neutralizing antibodies against botulinum neurotoxins, the Examiner has not articulated a finding that one of ordinary skill in the art could have pursued known potential solutions with a reasonable expectation of success. MPEP § 2143 guides that

if any of these findings cannot be made, then the exemplary rationale cannot be used to support a conclusion of obviousness.

Appellant has demonstrated that the Examiner's recitation of exemplary *KSR* bases for obviousness, namely that the instant method of treating subjects who already exhibit neutralizing antibodies against neurotoxin complexes with botulinum neurotoxin which is free of complexing proteins is "obvious to try", is not substantiated.

Appellant submits that the Examiner has not made of record prior art disclosure which fulfills the requirements of MPEP § 2143 interpretation of *KSR* and has capriciously misapplied *KSR* and has prejudicially misrepresented the art of record.

Appellant submits that the Examiner has failed to establish a factual basis for finding that the instant claims are obvious. Absent such showing, the Examiner has not met her burden to demonstrate that the rejected claims are *prima facie* obvious.

The Examiner's rejection should be reversed as failing to establish a *prima facie* case of obviousness.

3. Rejection of claims for obviousness over the disclosure of *Kessler, et al.* in view of *Johnson, et al.*

3.1 Appellant has rebutted *prima facie* obviousness on the basis that the cited art do not teach or suggest all claim limitations.

Appellant has demonstrated that the cited art, including *Johnson, et al.*, do not teach or suggest the instant generic claim limitation to a therapeutic method of

treatment with a botulinum neurotoxin preparation, "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes" at **Section C1a** beginning at page 33 of Appellant's Brief of October 7, 2008.

The Examiner does not provide comment with regard to Appellant's assertions in Section C1a, that the cited art do not teach or suggest the instant claim limitation, "wherein the human or animal already exhibits neutralizing antibodies against neurotoxin complexes".

The Examiner states on the record that *Kessler, et al.* do not teach the claim limitation "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes." (see the Examiner's Answer at page 38.)

Moreover, the Examiner has failed to identify where each of the specific limitations recited in the claims, for example, administering a botulinum neurotoxin preparation to a subject "wherein the human or animal subject already exhibits neutralizing antibodies against neurotoxin complexes", is found in the cited art (i.e., *Johnson, et al.)* in accord with MPEP § 1207. 02(A)(9)(d) and (e).

Appellant has demonstrated that *Johnson, et al.* do not teach or suggest the instant claim limitation to administering a botulinum neurotoxin to a subject "wherein the human or animal subject already exhibits neutralizing antibodies against neurotoxin complexes", and that the cited art is completely silent with respect to administering a botulinum neurotoxin composition to a subject, "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes."

The Examiner's rejection should be reversed for failing to demonstrate all claim limitations to be taught or suggested by the art. Absent such showing, the Examiner has not met her burden to demonstrate that the rejected claims are *prima facie* obvious after repeated solicitations from Appellant.

3.2 Appellant's claims are not *prima facie* obvious.

Moreover, the Examiner has not established a *prima facie* case of obviousness in view of the combined reference disclosures because the Examiner has not identified a suggestion or motivation to combine the teaching of the prior art references.

The Examiner concludes that, "*Johnson, et al.* recognize patients that have developed neutralizing antibodies to the complex are a growing concern in the art, thus this is the very bases for the development of compositions comprising 'essentially pure botulinum toxin'. Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex." (See Examiner's Answer at page 38.)

The Examiner does not articulate a factual basis to support a conclusion that, "Therefore, it would be obvious to administer these compositions to patents that have developed neutralizing antibodies to the botulinum toxin complex", and there surely is no suggestion in the art of record.

The Examiner opines that, "It is well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both *Kessler, et al.* and *Johnson, et al. Johnson, et al.* also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex. *Johnson, et al.* provided a solution to this problem, by preparing a product that is a pure

neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition." (See Examiner's Answer at page 39.)

Appellant does not dispute that *Johnson, et al.* developed compositions which are less antigenic to lessen the possibility of antibody formation, as acknowledged by the Examiner, which improvement overcomes the problem of developing neutralizing antibodies. To reject the claims for obviousness, the Examiner must establish that one skilled in the art actually has taught, or may infer from the combined disclosure of record, a solution for the efficacious treatment of subjects already exhibiting neutralizing antibodies against botulinum neurotoxin, which subjects the art of record are acknowledged, even by the Examiner, to be untreatable. In fact, it is this impossibility of treating which prompted *Johnson, et al.* to devise a method for avoiding the original generation of antibodies.

Significantly and critically, *Kessler, et al.* and *Johnson, et al.* do not teach or suggest the instant claim limitation to administration of *Clostridium botulinum* neurotoxin which is free of complexing proteins in subjects already exhibiting neutralizing antibodies. What is more, the cited art suggest that treatment of subjects already exhibiting neutralizing antibodies would not be successful.

Appellant has demonstrated that *Johnson, et al.* teach that, "A major drawback to the use of botulinum toxin in treatment of hyperactive muscle disorders is development of antibodies or other types of immunity by patients. The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders

with botulinum toxin ineffective." (See Column 1, lines 49-55, emphasis added.) Furthermore, the Examiner acknowledges that, "*Kessler, et al.* teach that at least one of the tests performed detected neutralizing serum antibodies in 9 of the 17 patients who clinically fulfilled the criteria for secondary nonresponse (page 217). *Kessler, et al.* teach that secondary nonresponse is one of the major problems in long-term treatment of CD with botulinum toxin A because it entails discontinuing, depriving the patient of the most successful therapy available (page 272)." (See Examiner's Answer at page 37.)

The cited art clearly teaches away from administering a botulinum neurotoxin in subjects already exhibiting neutralizing antibodies for the fact that the cited art discredits administration of botulinum neurotoxin, teaching discontinuing therapy in such subjects, thereby depriving the patient of the most successful therapy available.

The Examiner's stated position that, "Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex" finds no basis in the prior art disclosure of record, which, in fact is demonstrated to be contra-indicated.

The Examiner's rejection should be reversed as failing to establish a *prima facie* case of obviousness.

3.3 The Examiner misapplied and fails to substantiate a finding of obviousness under *KSR International Co. v. Teleflex Inc.*

The Examiner attempts to recite exemplary rationales to support a finding of obviousness. The Examiner states that "Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) discloses that if a technique has been used to improve one method and a person of ordinary skill would recognize that it

would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill." Furthermore, the Examiner states that, "*KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that 'The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.'" (See Examiner's Answer at pages 38 and 42).

The Examiner concludes that, "It is well known in the art to use botulinum toxin complex to treat dystonia or nervous system disorders. See *Kessler, et al.* It is also well known in the art that patients given high dosages of botulinum toxin complex over long periods of time develop neutralizing antibodies. See both *Kessler, et al.* and *Johnson, et al. Johnson, et al.* also recognized that there is a need in the art to solve the problem of the development of neutralizing antibodies to the botulinum toxin complex." (See Examiner's Answer at page 39, emphasis added.)

The Examiner goes on to conclude that, "*Johnson, et al.* provided a solution to this problem, by preparing a product that is a pure neurotoxin instead of the complex. Thus, it would be obvious to administer an essential pure composition of botulinum toxin (e.g. free of complexing proteins) to patients that have neutralizing antibodies because the composition of essentially pure botulinum toxin was developed to lessen or reduce the amount of neutralizing antibodies produced in patients after administration of the composition." (See Examiner's Answer at page 39, emphasis added.)

Furthermore, the Examiner goes on to conclude that, "In the instant case, there is a need in the art to find a solution to the problem of development of neutralizing antibodies in patents administered botulinum toxin complex over long periods of time. Since these patients exist there is the problem of treating these patients after botulinum toxin complex injection has failed. *Johnson, et al.* developed

compositions of essentially pure botulinum toxin to overcome these problems recognized in the prior art. This provides further support as to why one of skill in the art would administer a composition of essentially pure botulinum toxin to patents that have developed neutralizing antibodies to botulinum toxin complex." (See Examiner's Answer at pages 39-40, emphasis added.)

The Examiner and Appellant agree that *Johnson, et al.* developed botulinum neurotoxin preparations to overcome the problem of developing neutralizing antibodies.

The Examiner's conclusion, however, that, "one of skill in the art would administer a composition of essentially pure botulinum toxin to patients that have developed neutralizing antibodies" is not substantiated and is mere speculation by the Examiner.

Appellant submits that the Examiner has not articulated reasoning within the *KSR* guidelines as to why it would be obvious to administer a botulinum neurotoxin to subjects already exhibiting neutralizing antibodies based on the teaching of administering botulinum toxin without complexing proteins for preventing the development of neutralizing antibodies in *Johnson, et al.* Furthermore, the Examiner has not articulated a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable, in accord with *KSR* guidelines, particularly in view of the *Kessler, et al.* and *Johnson, et al.* teaching that patients who develop neutralizing antibodies no longer respond to botulinum toxin treatment and that botulinum neurotoxin therapy in these subjects is ineffective.

According to MPEP § 2143 interpreting *KSR*, the Examiner must demonstrate a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable. MPEP § 2143 guides that if this finding

cannot be made with respect to *KSR* exemplary rationales cited, then these rationales cannot be used to support a conclusion that the claims would have been obvious to one of ordinary skill in the art.

As discussed above, *Kessler, et al.* and *Johnson, et al.* teach that neutralizing antibodies directed against botulinum neurotoxins are the cause of therapeutic failure and that subjects who exhibit neutralizing antibodies would not benefit from treatment with botulinum neurotoxin, which teaching is acknowledged by the Examiner. The Examiner has, in fact, identified NO predictable solutions to the problem of treating subjects who already exhibit neutralizing antibodies.

Appellant submits that the Examiner's conclusion is precisely the product of an impermissible hindsight reconstruction. The Examiner has not provided any basis in fact nor identified predictable potential solutions to the problem of treating subjects already exhibiting neutralizing antibodies.

Furthermore, the Examiner reiterates the *KSR* exemplary basis as to why the claimed invention would have been obvious, concluding that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. (See Examiner's Answer at page 42.)

The Examiner concludes that, "In the instant case, compositions comprising botulinum toxin without complexing proteins are known in the art. See *Johnson, et al.* It is also known in the art that patients develop neutralizing antibodies. See both *Kessler, et al.* and *Johnson, et al.* It is known in the art to use botulinum toxin to treat cervical dystonia with botulinum toxin. See *Kessler, et al.* Thus, it would be obvious to use a known product in a known method that would

do more than yield predictable results." (See Examiner's Answer at pages 42-43.)

Appellant submits that the Examiner's second recitation of the exemplary *KSR* basis for obviousness is redundant on the same basis evaluated above and is no more substantiated. Absent demonstrated teaching to support the basis, Appellant rebuts the Examiner's rejection as without basis.

Appellant submits that the Examiner has not articulated a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable, which finding is required under MPEP § 2143 interpretation of the *KSR*.

Appellant has, however, demonstrated that an ordinary practitioner would not have expected or predicted that administering botulinum neurotoxin preparations to subjects who already exhibit neutralizing antibodies to botulinum neurotoxin would provide an effect in these subjects for the fact that the cited art teach that antibodies to botulinum toxins renders treatment with the toxin ineffective.

Furthermore, an exemplary rationale recited by the Examiner as to why the claimed invention would have been obvious in view of *KSR* is that it would be, "obvious to try". (See Examiner's Answer at pages 39 and 43.)

To support the exemplary rationale under *KSR*, the Examiner finds that, "In the instant case, it would be obvious to administer pure botulinum toxin to patients that have neutralizing antibodies because *Johnson, et al.* teach that the compositions of the invention reduces the chances of patients developing neutralizing antibodies." (See Examiner's Answer at page 44, emphasis added.)

According to MPEP § 2143 interpretation of *KSR,* to reject the claims based on the "obvious to try" exemplary rationale, the Examiner must articulate a finding that here had been a finite number of identified, predictable potential solutions to the recognized need or problem and that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success. Moreover, the Examiner is instructed to make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

In the instant case, such solutions are described in the claims to provide a means for treating patients exhibiting neutralizing antibodies. The Examiner has, in fact, identified NO predictable potential solutions to the problem of treating subjects who already exhibit neutralizing antibodies against neurotoxin complexes. As discussed above, the cited art teach that neutralizing antibodies directed against botulinum neurotoxin are the cause of therapeutic failure and that subjects who exhibit neutralizing antibodies would not benefit from treatment with botulinum neurotoxin, i.e., there are NO identified predictable potential solutions to the problem of treating subjects already exhibiting neutralizing antibodies to botulinum neurotoxin.

Not only has the Examiner failed to identify any predictable potential solutions to the problem of treating subjects who already exhibit neutralizing antibodies against neurotoxins, but also the Examiner has not articulated a finding that one of ordinary skill in the art could have pursued known potential solutions with a reasonable expectation of success. MPEP § 2143 guides that if any of these findings cannot be made, then the exemplary rationale cannot be used to support a conclusion of obviousness.

Appellant submits that the Examiner has not articulated reasoning within the *KSR* guidelines as to why it would be obvious to administer a botulinum neurotoxin to subjects already exhibiting neutralizing antibodies based on the teaching of

administering botulinum toxin without complexing proteins for preventing the development of neutralizing antibodies in *Johnson, et al.* Furthermore, the Examiner has not articulated a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable, in accord with *KSR* guidelines, particularly in view of the *Kessler, et al.* and *Johnson, et al.* teaching that patients who develop neutralizing antibodies no longer respond to botulinum toxin treatment.

Appellant has demonstrated that the Examiner's recitation of exemplary *KSR* bases for obviousness, namely that the instant method of treating subjects who already exhibit neutralizing antibodies against neurotoxin complexes with botulinum neurotoxin which is free of complexing proteins is "obvious to try", is not substantiated.

Appellant submits that the Examiner has not made of record prior art disclosure which fulfills the requirements of MPEP § 2143 interpretation of *KSR* and has capriciously misapplied *KSR* and has prejudicially misrepresented the art of record.

Appellant submits that the Examiner has failed to establish a factual basis for finding that the instant claims are obvious. Absent such showing, the Examiner has not met her burden to demonstrate that the rejected claims are *prima facie* obvious.

4. Rejection of claims for obviousness over the disclosure of *Göschel, et al.* in view of *Johnson, et al.*

4.1 Appellant has rebutted *prima facie* obviousness on the basis that the cited art do not teach or suggest all claim limitations.

The Examiner states on the record that *Göschel, et al.* do not teach the claim limitation, "wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes." (See Examiner's Answer at page 47.)

Appellant has demonstrated that the cited art, i.e., *Johnson, et al.*, do not teach or suggest the instant generic claim limitation to administering a botulinum neurotoxin preparation, "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes" at **Section D1a** beginning at page 42 of Appellant's Brief of October 7, 2008.

The Examiner does not provide comment with regard to Appellant's assertions in Section D1a, that the cited art do not teach or suggest the instant claim limitation, "wherein the human or animal already exhibits neutralizing antibodies against neurotoxin complexes".

Moreover, the Examiner has failed to identify where each of the specific limitations recited in the claims, for example, administering a botulinum neurotoxin preparation to a subject "wherein the human or animal subject already exhibits neutralizing antibodies against neurotoxin complexes", is found in the cited art (i.e., *Johnson, et al.)* in accord with MPEP § 1207. 02(A)(9)(d) and (e).

Appellant has demonstrated that *Johnson, et al.* do not teach or suggest the instant claim limitation to a therapeutic method of treatment with a botulinum neurotoxin preparation, "wherein the human or animal subject already exhibits neutralizing antibodies against neurotoxin complexes", which is discussed above. The Examiner acknowledges that *Göschel, et al.* do not teach the claim limitation, wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

Appellant has demonstrated that the cited art is completely silent with respect to administering a botulinum neurotoxin composition to a subject, "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes."

Appellant submits that the Examiner's rejection should be reversed for failing to demonstrate all claim limitations to be taught or suggested by the art. Absent such showing, the Examiner has not met her burden to demonstrate that the rejected claims are *prima facie* obvious after repeated solicitations from Appellant.

4.2 Appellant's claims are not *prima facie* obvious.

Moreover, the Examiner has not established a *prima facie* case of obviousness of the combined reference teachings because the Examiner has not identified a suggestion or motivation to combine the teaching of the prior art references.

The Examiner concludes that, "*Johnson, et al.* recognize patients that have developed neutralizing antibodies to the complex are a growing concern in the art, thus this is the very bases for the development of compositions comprising 'essentially pure botulinum toxin'. Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex." (See Examiner's Answer at page 47.)

The Examiner does not articulate a factual basis to support a conclusion that, "Therefore, it would be obvious to administer these compositions to patents that have developed neutralizing antibodies to the botulinum toxin complex."

Appellant does not dispute that *Johnson, et al.* developed compositions which are less antigenic to lessen the possibility of antibody formation. To reject the claims for obviousness, the Examiner must establish that one skilled in the art actually has taught, or may infer from the combined disclosure of record, the administration of *Clostridium botulinum* neurotoxin, which is free from complexing proteins, for the efficacious treatment of subjects already exhibiting neutralizing antibodies against botulinum neurotoxins.

Appellant has demonstrated that *Johnson, et al.* teach that, "A major drawback to the use of botulinum toxin in treatment of hyperactive muscle disorders is development of antibodies or other types of immunity by patients. The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective." (See Column 1, lines 49-55, emphasis added.) Furthermore, the Examiner acknowledges that, "*Göschel, et al.* teach that neutralizing antibodies were the cause of therapeutic failure (page 101)." (See Examiner's Answer at pages 46-47, emphasis added.)

Göschel, et al. and *Johnson, et al.* teach that administration of botulinum neurotoxin compositions to subjects already exhibiting neutralizing antibodies against botulinum neurotoxin complexes would not be successful. Therefore, there is no teaching in the cited art which would provide one skilled in the art with any motivation to administer a botulinum neurotoxin composition with the expectation that such composition would provide efficacy in subjects already exhibiting neutralizing antibodies.

The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783, F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986)

Appellant submits that the factual information in the art of record regarding the ineffectiveness of botulinum neurotoxin treatment in subjects with neutralizing antibodies against botulinum neurotoxins, as discussed above, demonstrates that the Examiner's stated position that, "Therefore, it would be obvious to administer these compositions to patients that have developed neutralizing antibodies to the botulinum toxin complex" finds no basis in the prior art disclosure of record, and supports the nonobviousness of the instant invention.

The Examiner's rejection should be reversed as failing to establish a *prima facie* case of obviousness.

4.3 The Examiner misapplied and fails to substantiate a finding of obviousness under *KSR International Co. v. Teleflex Inc.*

The Examiner attempts to recite exemplary rationales to support a finding of obviousness. The Examiner states that "Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) discloses that if a technique has been used to improve one method and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill." Furthermore, the Examiner states that, "*KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that 'The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.'" (See Examiner's Answer at pages 47, 48 and 51).

The Examiner concludes that, "In the instant case, compositions comprising botulinum toxin without complexing proteins are known in the art. See *Johnson, et al.* It is also known in the art that patients develop neutralizing antibodies. See both, *Göschel, et al.* and *Johnson, et al.* It is known in the art to use botulinum toxin to treat torticollis spasmodicus, facial dystonias, torsion dystonia

and spasticity patients. See *Göschel, et al.* Thus, it would be obvious to use a known product in a known method that would do more than yield predictable results." (See Examiner's Answer at page 52.)

Appellant submits that the Examiner's recitation of exemplary *KSR* bases for obviousness, namely that, "it would be obvious to apply a known technique to a known product that is ready for improvement to yield predictable results." is nothing more than speculation and finds no basis in the prior art disclosure of record. Absent demonstrated teaching to support the basis, Appellant rebuts the Examiner's rejection as without basis.

Combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. *United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 483-84 (1966).

According to MPEP § 2143 interpreting *KSR*, the Examiner must demonstrate a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable. MPEP § 2143 guides that if this finding cannot be made with respect to *KSR* exemplary rationales cited, then these rationales cannot be used to support a conclusion that the claims would have been obvious to one of ordinary skill in the art.

Appellant submits that the Examiner has not articulated a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable, which finding is required under the *KSR* guidelines at MPEP § 2143.

Appellant has, however, demonstrated that an ordinary practitioner would not have expected or predicted that administering botulinum neurotoxin preparations

to subjects who already exhibit neutralizing antibodies to botulinum neurotoxins would provide an effect in these subjects.

Appellant has demonstrated that efficacious treatment of subjects already exhibiting neutralizing antibodies to botulinum neurotoxins may not be predicted based on the teaching of the cited art, *Göschel, et al.* and *Johnson, et al.* As acknowledged by the Examiner, *Johnson, et al.* teach that antibodies to botulinum toxin renders treatment with botulinum toxin ineffective and that *Göschel, et al.* teach that neutralizing antibodies are the cause of therapeutic failure. Therefore, based on the teaching of the cited art, an ordinary practitioner would have not have expected or predicted that administering botulinum neurotoxin preparations to subjects who already exhibit neutralizing antibodies to botulinum neurotoxins would provide an effect in these subjects.

Furthermore, an exemplary rationale recited by the Examiner as to why the claimed invention would have been obvious in view of *KSR* is that it would be, "obvious to try". (See Examiner's Answer at pages 48 and 52.)

To support the exemplary rationale, the Examiner finds that, "In the instant case, it would be obvious to administer pure botulinum toxin to patients that have neutralizing antibodies because *Johnson, et al.* teach that the compositions of the invention reduces the chances of patients developing neutralizing antibodies." (See Examiner's Answer at page 53, emphasis added.)

According to MPEP § 2143 interpretation of *KSR,* to reject the claims based on the "obvious to try" exemplary rationale to support a finding of obviousness, the Examiner is required to articulate a finding that here had been a finite number of identified, predictable potential solutions to the recognized need or problem and that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success. Moreover, the Examiner is

instructed to make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

In the instant case, such solutions are described in the claims to provide a means for treating patients exhibiting neutralizing antibodies. The Examiner has, in fact, identified NO predictable potential solutions to the problem of treating subjects who already exhibit neutralizing antibodies against neurotoxin complexes. As discussed above, the cited art teach that neutralizing antibodies directed against botulinum neurotoxin are the cause of therapeutic failure and that subjects who exhibit neutralizing antibodies would not benefit from treatment with botulinum neurotoxin, i.e., there are NO identified predictable potential solutions to the problem of treating subjects already exhibiting neutralizing antibodies to botulinum neurotoxin.

Appellant submits that the Examiner's conclusion is precisely the product of an impermissible hindsight reconstruction. The Examiner has not provided any basis in fact as to why one skilled in the art would administer botulinum neurotoxin in view of the prior art teaching that such administration would not be effective, nor has the Examiner identified predictable potential solutions to the problem of treating subjects already exhibiting neutralizing antibodies.

Not only has the Examiner failed to identify any predictable potential solutions to the problem of treating subjects who already exhibit neutralizing antibodies against neurotoxin complexes, but also the Examiner has not articulated a finding that one of ordinary skill in the art could have pursued known potential solutions with a reasonable expectation of success. MPEP § 2143 guides that if any of these findings cannot be made, then the exemplary rationale cannot be used to support a conclusion of obviousness.

Appellant has demonstrated that the Examiner's recitation of exemplary *KSR* bases for obviousness, namely that the instant method of treating subjects who already exhibit neutralizing antibodies with botulinum neurotoxin which is free of complexing proteins is "obvious to try", is not substantiated.

Appellant submits that the Examiner has not made of record prior art disclosure which fulfills the requirements of MPEP § 2143 interpretation of *KSR* and has capriciously misapplied *KSR* and has prejudicially misrepresented the art of record.

The Examiner's rejection should be reversed as failing to establish a *prima facie* case of obviousness.

CONCLUSION

In summary, Appellant submits that the Examiner's continued rejection of the claims for obviousness, despite Appellant's repeated demonstrations that the cited art do not teach or suggest all claim limitations and that the cited art do not motivate one skilled in the art to combine the references' teaching with a reasonable expectation of success, is based upon a faulty understanding of well established case law and the statutory function of the claims as well as an arbitrary and capricious misinterpretation of the art of record. From this faulty legal and factual analysis, the Examiner fails to give proper and due consideration to Appellant's rebuttal arguments and evidence which, when properly considered as required by the case law, rebut any *prima facie* rejection for obviousness. Moreover, the Examiner's Answer is non-compliant with MPEP guidelines for the same and, consequently, is prejudicial to Appellant's ability to rebut what arguments/opinions the Examiner may have.

The Examiner's Answer is non-compliant with the MPEP, and therefore, the Examiner's bases for rejection should be disregarded. Moreover, Appellant submits that the Examiner's obviousness rejections are improper and should be reversed.

If necessary, the Commissioner is hereby authorized in this, to charge any further or additional fees which may be required (due to omission, deficiency, or otherwise), or to credit any overpayment, to Deposit Account No. 08,3220.

Respectfully submitted:

THE FIRM OF HUESCHEN AND SAGE

By: _____

G. PATRICK SAGE, #37,710

THE FIRM OF HUESCHEN AND SAGE

By: _____

KATHERINE L. WEILAND, #56,942

Dated: March 4, 2009
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